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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/747,825	12/22/2000	Stephen Grimes	1102865-0036	4304

7470 7590 06/05/2003

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EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	16

DATE MAILED: 06/05/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/747,825	Applicant(s) GRIMES ET AL.	
	Examiner Phuong Huynh	Art Unit 1644	

-- Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 March 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *35,38,40,41,43,44 and 46-72* is/are pending in the application.

4a) Of the above claim(s) *62-72* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35,38,40,41,43,44 and 46-72* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 35, 38, 40-41, 43-44, and 46-72 are pending.

2. In view of the amendment filed 3/24/03, the following rejections remain.

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 35, 38, 41 and 44 stand rejected under 35 U.S.C. 102(b) as being anticipated by US Pat No 5,424,067 (of record, June 1995, PTO 1449).

The '067 patent teaches an immunogenic composition such as a vaccine formulated in an emulsion comprising an oily vehicle such as squalene, squalane and spermaceti oil and the aqueous phase (buffer) containing any antigen such as Influenza virus in addition to lecithin and PEG monooleate as emulsifier (See abstract, column 3, lines 31-33, in particular). The reference composition is stable for at least 12 months and over a year in storage at 4°C (See abstract, column 4, line 24, claims 1, 2, 5 of the '067 patent, in particular). The reference composition is formulated as a mixture of water (buffer) in oil in water multiphase solutions (W/O/W) (See abstract, in particular). The term "comprising" is open-ended. It expands the claimed immunogenic composition to include additional compound in the composition. The reference composition is stable in cold storage and in freezing temperature because of the inherent property of the reference squalene and squalane. Claim 44 is included in this rejection because the claimed composition appears to be the same as the reference composition and the increased in immunogenicity upon storage is an inherent properties of the reference composition because the reference squalene and squalane are oil which have the characteristics of adjuvant such as increase antibody level in mice (See column 4, line 49-51, in particular). The recitation of an emulsion which is stable in frozen storage has no patentable weight because a composition is a composition, irrespective of where the composition is being stored. Further, all composition appears to stable in frozen storage. The recitation of the thawed composition retaining at least 60% of the emulsion globules at a size of less than 1μm and exhibiting a normal release rate of

the immunogen are the inherent properties of the reference emulsion composition. The '067 patent further teaches additional immunogenic composition formulated in water in oil emulsion such as formula 4A without emulsion stabilizer such as PEG 500 and the reference emulsion at 20°C (thawed temperature) has globules size of about 1 μm. The reference "about" reads on the claimed less than 1μm (See column 7, Table 4-1, in particular). Thus, the reference teachings anticipate the claimed invention.

Applicants' arguments filed 3/24/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) the reference is silent on frozen storage of vaccine emulsions. (2) The claimed bispecific composition is either a water-in-oil or oil-in-water ruling out the reference's selection of only multiphasic W/O/W emulsion. (3) The cited disclosure of the '067 patent actually teaches away from the instant biphasic system by declaring it as vaccine-ineffective (see reference example 4, Table 4-2). (4) The specification discloses in table 7 that the W-O-W emulsion is not stable after e.g., -23°C and -70°C freeze-thaw cycling (5 cycles). (5) There is no disclosure as whether the cited emulsion were stored over 12 months at 4°C before for vaccination. (6) only certain pharmaceutically acceptable oily vehicle species have been found among those tested suitable for long-term frozen storage at temperature ranging from -18 to -80°C or multiple freeze/thaw cycling (page 4, line 24-25, also table 7 of specification).

However, none of the instant claims 35, 41 and 44 recite "water-in-oil or oil-in-water" emulsion. The claimed composition appears to be the same immunogenic composition formulated as an emulsion of the reference. Since the Patent Office does not have the facilities for examining and comparing the antibodies of the instant invention to those of the prior art, the burden is on applicant to show that the prior art immunogenic composition formulated as an emulsion is different from the claimed immunogenic composition. See In re Best, 562 F.2d 1252, 195 USPQ 430(CCPA 1977).

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., -23°C and -70°C freeze-thaw cycling (5 cycles) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

In response to applicant's argument that there is no disclosure as whether the cited emulsion were stored over 12 months at 4°C before for vaccination, a recitation of the intended

use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963).

In response to applicant's argument that only certain pharmaceutically acceptable oily vehicle species have been found among those tested suitable for long-term frozen storage at temperature ranging from -18°C to -80°C or multiple freeze/thaw cycling, it is noted that the features upon which applicant relies (i.e., -18°C and -70°C freeze-thaw cycling (5 cycles) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Further, the certain species of oily vehicle suitable for long-term storage such as ISA 703 is squalene and squalane are taught by the' 067 patent (See claim 5 of '067 patent, in particular).

5. Claims 49-52 stand rejected under 35 U.S.C. 102(b) as being anticipated by US Pat No. 5,468,494 A (of record, Nov 1995, PTO 1449).

The '494 patent teaches an immunogenic composition comprising an emulsion such as oily vehicle Montanide ISA type 703 and an aqueous immunogen such as gastrin 17 conjugated to an immunogenic carrier such as diphtheria toxoid, tetanus toxoid and keyhole limpet hemocyannin in PBS and aluminum monostereate (See column 4, example 4, claims 1-5 of '494 patent, in particular). The '494 patent further teaches a method for formulating the reference immunogenic composition by mixing an aqueous immunogen such as gastrin 17, which is a hormone immunomimic peptide fragment, coupled to an immunogenic carrier such as DT in PBS with a pharmaceutically acceptable oily vehicle in an oil-in-water or water-in-oil formulation wherein the suitable oily vehicle is Montanide type ISA 703 (See column 4, lines 25-65, in particular). The reference method of formulating the reference immunogenic composition is stable in storage for a minimal of several weeks, which is more than one day or at least one month (see column 4, lines 37-40, in particular). The term "comprising" is open-ended. It expands the claimed immunogenic composition to include additional compound in the composition. The claimed composition appears to be the same as the reference composition. The reference

composition is stable in cold storage that can last at least 8 days, a year, or in freezing temperature because of the inherent property of the reference mineral oil, Montanide type ISA 703. The increase in immunogenicity upon storage is also an inherent property of the reference mineral oily vehicle Montanide type ISA 703 in composition. Claims 50-52 are included in this rejection because the integrity of the reference composition is an inherent property of the reference mineral oil Montanide type ISA 703 in the reference composition. Thus, the reference teachings anticipate the claimed invention.

Applicants' arguments filed 3/24/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) the cited patent discloses an aqueous solution containing the G17 peptide: DT conjugate together with or without nor-MDP adjuvant, containing AMS. The cited composition and the method of making the composition is prepared by mixing an aqueous phase 1:1 Montanide ISA 703 oily phase to aluminum monostearate (AMS) is added as requisite emulsion stabilizer, the emulsion of the claimed composition and method of making the claimed composition does not contain any additional exogenous stabilizer. Further, Montanide ISA 703 is mixed in the W/O emulsion at a 30/70 ratio.

However, claim 45 recites a method for formulating an immunogenic composition suitable for cold storage comprising: preparing an immunogenic emulsion comprising mixing an aqueous immunogen with a pharmaceutically acceptable oily vehicle in an oil-in-water or water-in-oil formulation, wherein the suitable oil is selected from the group consisting of SBAS3, and a Montanide type ISA 25, ISA 28D, ISA 206, ISA 206D, ISA 703 and ISA 720.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., exogenous stabilizer and the W/O emulsion 30/70 ratio) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Further, the term comprising is open-ended. It expands the method of formulating an immunogenic composition to include additional component such as aluminum monostearate (AMS) is added as requisite emulsion stabilizer.

6. The following new grounds of rejection are necessitated by the amendment filed 3/24/03.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 35, 38, 40-41, 43-44, and 46-72 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) an immunogenic composition formulated as an emulsion which is stable in frozen storage at -18°C or -70°C comprising an aqueous phase immunogen wherein the immunogen is selected from the group consisting of consisting of gastrin-17 (G17), gastrin-34 (G34) and gonadotropin releasing hormone conjugated to an immunogenic carrier protein optionally linked through a spacer peptide and a pharmaceutically acceptable oily vehicle selected from the group consisting of Montanide type ISA 25, ISA 703, ISA 719 and ISA 720, without an additional emulsion stabilizer; and wherein the globular size distribution of the emulsion is at least 97% less than 1μm in size after five successive freeze thaw cycles and the immunogen exhibits normal release rate from the emulsion, (2) the said immunogenic composition is formulated as a mixture of the oily vehicle and the aqueous phase immunogen at a ratio of 70: 30 oil to aqueous phase so as to form an oil-in-water or water-in-oil emulsion, (3) the said immunogenic composition wherein the oily vehicle is Montanide type ISA 703, (4) A method for formulating an immunogenic composition stable at in frozen storage at -18 or -70°C comprising: preparing an immunogenic emulsion by mixing an aqueous phase immunogen selected from the group consisting of consisting of gastrin-17 (G17), gastrin-34 (G34) and gonadotropin releasing hormone conjugated to an immunogenic carrier protein optionally linked through a spacer peptide and a pharmaceutically acceptable oily vehicle selected from the group consisting of Montanide type ISA 25, ISA 703, ISA 719 and ISA 720 at a ratio of 70: 30 oil to aqueous phase so as to form a stable oil-in-water or water-in-oil formulation without an additional emulsion stabilizer and wherein the globular size distribution of the emulsion is at least 97% less than 1μm in size after five successive freeze thaw cycles and the immunogen exhibits normal release rate from the emulsion, (5) the said method wherein the integrity of the immunogenic emulsion comprises a prolonged integrity of the immunogen, (6), the said method wherein the integrity is preserved for more than one week, more than one month, or more than one year, **does not** reasonably provide enablement for:

(1) *any* immunogenic composition formulated as an emulsion which is stable in frozen storage comprising *any* aqueous phase immunogen and a pharmaceutically acceptable oily

vehicle selected from the group consisting of the Montanide ISA 25, ISA 703, ISA 719 and ISA 720, without an additional emulsion stabilizer; the thawed composition retaining at least 60% of the emulsion globules at a size of less than 1 μm and exhibiting a normal release rate of any immunogen,

(2) the said immunogenic composition wherein the emulsion is formulated as a mixture of the oily vehicle and the aqueous phase immunogen so as to form an oil-in-water or water-in-oil emulsion,

(3) the said immunogenic composition wherein the oily vehicle is Montanide type ISA 703,

(4) the said immunogenic composition wherein the frozen storage can last at least one year or at least 8 days,

(5) *any* immunogenic composition formulated as an emulsion which is stable in frozen storage comprising any aqueous phase immunogen and a pharmaceutically acceptable oily vehicle selected from the group consisting of the Montanide ISA 25, ISA 703, ISA 719 and ISA 720, without an additional emulsion stabilizer; the thawed composition retaining at least 60% of the emulsion globules at a size of less than 1 μm and exhibiting a normal release rate of any immunogen wherein the aqueous immunogen comprises *any* gastrin-17 (G17), *any* gastrin-34 (G34) or *any* "gonadotropin releasing hormone immunomimic peptide" conjugated to any immunogenic carrier protein optionally linked through a spacer peptide,

(6) the said immunogenic composition wherein the composition significantly increased immungenicity after one freezing thawing cycle,

(7) A method of formulating any immunogenic composition suitable for cold storage comprising: preparing an immunogenic emulsion comprising mixing *any* aqueous immunogen with a pharmaceutically acceptable oily vehicle in oil-in-water or water-in-oil formulation, wherein the pharmaceutically acceptable oily vehicle selected from the group consisting of the Montanide ISA 25, ISA 703, ISA 719 and ISA 720,

(8) A method for formulating any immunogenic composition stable in frozen storage comprising preparing any immunogenic emulsion by mixing an aqueous phase immunogen comprising an immunogenic carrier conjugated to *any* "immunomimic peptide", with a pharmaceutically acceptable oily vehicle so as to form a stable frozen storage oil-in-water or water-in-oil formulation wherein the oily vehicle is selected from the group consisting of the Montanide ISA 25, ISA 703, ISA 719 and ISA 720 without an additional emulsion stabilizer; the

thawed composition retaining at least 60% of the emulsion globules at a size of less than 1 μm and exhibiting a normal release rate of any immunogen,

(9) the said method wherein the immunogen comprises *any* synthetic "immunogenic peptide" conjugated to *any* immunogenic carrier "component",

(10) the methods mentioned above wherein the peptide "comprises" *any* epitope of gastrin 17 (G17), gastrin 34 (G34) or GnRH,

(11) the methods mentioned above wherein the storage stability of the immunogenic emulsion comprises a prolonged integrity of the immunogen,

(12) the methods mentioned above wherein is preserved for more than one week, more than one month, or more than one year,

(13) *any* immunogenic composition formulated as an oil-in-water or water-in-oil emulsion which is stable in frozen storage comprising an aqueous phase immunogenic carrier conjugated to *any* "G17 immunomimic peptide", and a pharmaceutically acceptable oily vehicle at a ratio of 30:70, consisting of Montanide ISA 703, without an additional emulsion stabilizer, the thawed composition retaining at least 60% of the emulsion globules at a size of less than 1 μm and exhibiting a normal release rate of any immunogen,

(14) the immunogenic composition formulated as an oil-in-water or water-in-oil emulsion which is stable in frozen storage comprising an aqueous phase immunogenic carrier conjugated to *any* "G17 immunomimic peptide", and a pharmaceutically acceptable oily vehicle at a ratio of 30:70, consisting of Montanide ISA 703, without an additional emulsion stabilizer, the thawed composition retaining at least 60% of the emulsion globules at a size of less than 1 μm and exhibiting a normal release rate of any immunogen wherein the immunogen remains substantially intact after prolonged frozen storage, the integrity of the immunogen is not significantly affected after one or more freeze-thaw cycles, wherein at lest 97% of the emulsion maintains a globule size of less than 1μm after five successive five freeze-thaw cycles,

(15) the immunogenic compositions mentioned above wherein the composition is *any* "synthetic immunomimic peptide" conjugated to an immunogenic carrier,

(16) the immunogenic compositions mentioned above wherein the composition is stored at about -18 °C to about -80°C, or at about -18°C to about -23°C, or at about -70°C,

(17) A method for formulating any immunogenic composition stable in frozen storage comprising preparing any immunogenic oil-in-water and water-in-oil emulsion by mixing any aqueous phase immunogen comprising an immunogenic carrier conjugated to *any* "G17

immunomimic peptide", any "immunomimic peptide", *any* "immunomimic peptide comprises *any* epitope of gastrin 17, gastrin 34 or GnRH" with a pharmaceutically acceptable oily vehicle selected from the group consisting of the Montanide ISA 25, ISA 703, ISA 719 and ISA 720, without an additional emulsion stabilizer; the thawed composition retaining at least 60% of the emulsion globules at a size of less than 1 μm and exhibiting a normal release rate of any immunogen for frozen emulsion which protects the immunogen during long-term storage. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only an immunogenic composition formulated as an emulsion which is stable in frozen storage at -18°C or -70°C comprising an aqueous phase immunogen wherein the immunogen is selected from the group consisting of gastrin-17 (G17), gastrin-34 (G34) and gonadotropin releasing hormone conjugated to an immunogenic carrier protein optionally linked through a spacer peptide and a pharmaceutically acceptable oily vehicle selected from the group consisting of Montanide type ISA 25, ISA 703, ISA 719 and ISA 720, without an additional emulsion stabilizer; and wherein the globular size distribution of the emulsion is at least 97% less than 1μm in size after five successive freezing thawing cycles and the immunogen exhibits normal release rate from the emulsion. The immunogenic composition is formulated as a mixture of the oily vehicle and the aqueous phase immunogen that is at a ratio of 70:30 oil to aqueous phase so as to form an oil-in-water or water-in-oil emulsion. The specification also discloses a method for formulating said immunogenic composition.

The specification does not teach how to make and use *any* immunogenic composition mentioned above comprising any aqueous phase immunogen because *any* immunogen, *any* immunomimic peptide, *any* synthetic immunomimic peptide conjugated to an immunogenic carrier, *any* immunomimic peptide comprises any epitope of gastrin 17, gastrin 34 or GnRH

without the specific amino acid sequence has no structure, much less function. Further, the term "comprises" in claim 71 is open-ended. It expands the undisclosed epitope of gastrin 17, gastrin 34 or GnRH to include additional amino acids at either or both ends. There is insufficient guidance as to the specific amino acids to be added and whether the resulting epitope would maintain the same structure and function as gastrin 17, gastrin 34 or GnRH, in turn, would be useful for an immunogenic composition that generates antibody specific for gastrin 17, gastrin 34 or GnRH.

Stryer *et al* teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages).

Ngo *et al* teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

Kuby *et al* teach that antibody epitopes (B cell epitopes) are not linear and are comprised of complex three-dimensional array of scattered residues which will fold into specific conformation that contribute to binding (See Kuby 1994, page 94, in particular). Immunization with a peptide fragment derived from a full-length polypeptide may result in antibody specificity that differs from the antibody specificity directed against the native full-length polypeptide. Without the specific amino acid residues, it is unpredictable which undisclosed peptide would generate antibody that is specific for any given epitope of gastrin 17, gastrin 34 or GnRH.

Abaza *et al* teach that even a single amino acid substitution outside the antigenic site can exert drastic effects on the reactivity of a protein with monoclonal antibody against the site (See abstract, in particular). Given the indefinite number of undisclosed immunogen, immunomimic peptide such as immunomimic peptide comprises any epitope of gastrin 17, gastrin 34 or GnRH, and synthetic immunomimic peptide, it is unpredictable which undisclosed immunogen in the claimed immunogenic composition would generate antibody specific for gastrin 17, gastrin 34 or GnRH.

Even if the immunogen is limited to gastrin 17, gastrin 34 or GnRH, there is insufficient guidance and working example demonstrating that *any* ratio of oil to the aqueous phase immunogen would result in a thawed composition retaining at least 60% or at least 97% of the emulsion globules size of less than 1 μm and exhibiting a normal release rate of the immunogen

after five successive freezing-thawing cycles or after prolonged frozen storage. As asserted by Applicant on page 12 of the response, the stability of the emulsion is due to its association with the aqueous phase solution which exerts an inter active effect by freezing and thawing at different lower temperature range than the oily vehicle. The skilled artisan would expect that a freezing temperature as well as thawing out would affect the aqueous phase component of differently than the oily phase, due to different physical properties. As asserted by Applicant on page 14 of the response that the emulsion globules containing aqueous components which coexists in an oily continuous phase are not reasonably predictable after freezing as it relates to resistance against undesirable changes in globule size by coalescence into two separate phase layers so as to form undesirable large globule sizes (> 1 μm). Since the immunogen and the ratio of the oil-in-water in the immunogenic composition is not enabled, it follows that the stability and integrity of the immunogenic composition are not enabled. It also follows that the method of making the undisclosed immunogenic composition is not enabled.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

9. Claims 35, 38, 40-41, 43-44, and 46-72 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) *any* immunogenic composition formulated as an emulsion which is stable in frozen storage comprising *any* aqueous phase immunogen and a pharmaceutically acceptable oily vehicle selected from the group consisting of the Montanide ISA 25, ISA 703, ISA 719 and ISA 720, without an additional emulsion stabilizer; the thawed composition retaining at least 60% of the

emulsion globules at a size of less than 1 μm and exhibiting a normal release rate of any immunogen,

(2) the said immunogenic composition wherein the emulsion is formulated as a mixture of the oily vehicle and the aqueous phase immunogen so as to form an oil-in-water or water-in-oil emulsion,

(3) the said immunogenic composition wherein the oily vehicle is Montanide type ISA 703,

(4) the said immunogenic composition wherein the frozen storage can last at least one year or at least 8 days,

(5) *any* immunogenic composition formulated as an emulsion which is stable in frozen storage comprising any aqueous phase immunogen and a pharmaceutically acceptable oily vehicle selected from the group consisting of the Montanide ISA 25, ISA 703, ISA 719 and ISA 720, without an additional emulsion stabilizer; the thawed composition retaining at least 60% of the emulsion globules at a size of less than 1 μm and exhibiting a normal release rate of any immunogen wherein the aqueous immunogen comprises *any* gastrin-17 (G17), *any* gastrin-34 (G34) or *any* "gonadotropin releasing hormone immunomimic peptide" conjugated to any immunogenic carrier protein optionally linked through a spacer peptide,

(6) the said immunogenic composition wherein the composition significantly increased immungenicity after one freezing thawing cycle,

(7) A method of formulating any immunogenic composition suitable for cold storage comprising: preparing an immunogenic emulsion comprising mixing *any* aqueous immunogen with a pharmaceutically acceptable oily vehicle in oil-in-water or water-in-oil formulation, wherein the pharmaceutically acceptable oily vehicle selected from the group consisting of the Montanide ISA 25, ISA 703, ISA 719 and ISA 720,

(8) A method for formulating any immunogenic composition stable in frozen storage comprising preparing any immunogenic emulsion by mixing an aqueous phase immunogen comprising an immunogenic carrier conjugated to *any* "immunomimic peptide", with a pharmaceutically acceptable oily vehicle so as to form a stable frozen storage oil-in-water or water-in-oil formulation wherein the oily vehicle is selected from the group consisting of the Montanide ISA 25, ISA 703, ISA 719 and ISA 720 without an additional emulsion stabilizer; the thawed composition retaining at least 60% of the emulsion globules at a size of less than 1 μm and exhibiting a normal release rate of any immunogen,

(9) the said method wherein the immunogen comprises *any* synthetic "immunogenic peptide" conjugated to *any* immunogenic carrier "component",

(10) the methods mentioned above wherein the peptide "comprises" *any* epitope of gastrin 17 (G17), gastrin 34 (G34) or GnRH,

(11) the methods mentioned above wherein the storage stability of the immunogenic emulsion comprises a prolonged integrity of the immunogen,

(12) the methods mentioned above wherein is preserved for more than one week, more than one month, or more than one year,

(13) *any* immunogenic composition formulated as an oil-in-water or water-in-oil emulsion which is stable in frozen storage comprising an aqueous phase immunogenic carrier conjugated to *any* "G17 immunomimic peptide", and a pharmaceutically acceptable oily vehicle at a ratio of 30:70, consisting of Montanide ISA 703, without an additional emulsion stabilizer, the thawed composition retaining at least 60% of the emulsion globules at a size of less than 1 μm and exhibiting a normal release rate of any immunogen,

(14) the immunogenic composition formulated as an oil-in-water or water-in-oil emulsion which is stable in frozen storage comprising an aqueous phase immunogenic carrier conjugated to *any* "G17 immunomimic peptide", and a pharmaceutically acceptable oily vehicle at a ratio of 30:70, consisting of Montanide ISA 703, without an additional emulsion stabilizer, the thawed composition retaining at least 60% of the emulsion globules at a size of less than 1 μm and exhibiting a normal release rate of any immunogen wherein the immunogen remains substantially intact after prolonged frozen storage, the integrity of the immunogen is not significantly affected after one or more freeze-thaw cycles, wherein at lest 97% of the emulsion maintains a globule size of less than 1μm after five successive five freeze-thaw cycles,

(15) the immunogenic compositions mentioned above wherein the composition is *any* "synthetic immunomimic peptide" conjugated to an immunogenic carrier,

(16) the immunogenic compositions mentioned above wherein the composition is stored at about -18 °C to about -80°C, or at about -18°C to about -23°C, or at about -70°C,

(17) A method for formulating any immunogenic composition stable in frozen storage comprising preparing any immunogenic oil-in-water and water-in-oil emulsion by mixing any aqueous phase immunogen comprising an immunogenic carrier conjugated to *any* "G17 immunomimic peptide", any "immunomimic peptide", *any* "immunomimic peptide comprises *any* epitope of gastrin 17, gastrin 34 or GnRH" with a pharmaceutically acceptable oily vehicle

selected from the group consisting of the Montanide ISA 25, ISA 703, ISA 719 and ISA 720, without an additional emulsion stabilizer; the thawed composition retaining at least 60% of the emulsion globules at a size of less than 1 μm and exhibiting a normal release rate of any immunogen for frozen emulsion which protects the immunogen during long-term storage.

The specification discloses only an immunogenic composition formulated as an emulsion which is stable in frozen storage at -18°C or -70°C comprising an aqueous phase immunogen wherein the immunogen is selected from the group consisting of gastrin-17 (G17), gastrin-34 (G34) and gonadotropin releasing hormone conjugated to an immunogenic carrier protein optionally linked through a spacer peptide and a pharmaceutically acceptable oily vehicle selected from the group consisting of Montanide type ISA 25, ISA 703, ISA 719 and ISA 720, without an additional emulsion stabilizer; and wherein the globular size distribution of the emulsion is at least 97% less than 1μm in size after five successive freezing thawing cycles and the immunogen exhibits normal release rate from the emulsion. The immunogenic composition is formulated as a mixture of the oily vehicle and the aqueous phase immunogen at a ratio of 70:30 oil to aqueous phase so as to form an oil-in-water or water-in-oil emulsion. The specification also discloses a method for formulating said immunogenic composition.

With the exception of the specific immunogenic composition and the specific method of making the specific immunogenic composition, there is insufficient written description about the structure associated with function of any aqueous phase immunogen such as *any* "immunomimic peptide" conjugated to an immunogenic carrier, *any* immunomimic peptide conjugated to any "immunogenic carrier component", *any* gastrin-17(G17) immunomimic peptide, *any* gastrin-34 (G34) immunomimic peptide, *any* gonadotropin releasing hormone immunomimic peptide, *any* immunomimic peptide comprises any epitope of gastrin 17, gastrin 34 or GnRH because the terms "immunogen", "peptide", and "component" without the amino acid sequence have no structure, let alone the peptide can mimic the immune response of gastrin-17(G17), gastrin 34 or GnRH. Further, the term "comprises" is open-ended. Not only the epitope is not defined, the term "comprises" expands the undisclosed epitope of gastrin 17, gastrin 34 or GnRH to include additional amino acid at either or both ends. Given the indefinite number of undisclosed immunogen, the immunogenic composition as well as the method of making such undisclosed immunogenic composition is not adequately described.

Further, the specification discloses only three immunogens such as gastrin 17, gastrin 34 an GnRH and only one ratio of 70:30 oil to aqueous phase so as to form an oil-in-water or water-

in-oil emulsion that retains at least 60% or at least 97% of the emulsion globules at a size of less than 1 μm as encompassed by the claimed immunogenic composition and the method of making the same composition, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

10. Claims 59-61, and 65-72 are rejected under 35 U.S.C. 112, first paragraph, containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection**.

The "about" in Claims 59-61, 65-68 represents a departure from the specification and the claims as originally filed. The term expands the upper and lower range to temperature in said claims. Applicant has not pointed out the support for said phrase "about".

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

12. Claim 41 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "cold storage" in claim 41 has no antecedent basis in base claims 36 and 37, respectively, because the word "cold" is not recited in claim 36 and 37.

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 35, 38, 40-41 and 49-52 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 90/14837 publication (December 1990, PTO 1449).

The WO 90/14837 publication teaches a method of making an immunogenic composition formulated as an emulsion which is stable in frozen storage at zero degree comprising an aqueous phase immunogen such as MTP-PE-LO (Formulation M) and a pharmaceutically acceptable oily vehicle such as squalene which is a metabolizable oil in the Montanide type ISA 703, without an additional emulsion stabilizer such as AMS (See table 8, page 44, in particular). The reference emulsion having oil droplets substantially all of which are less than less than 1 μm (See Table 8 on page 44, summary of invention, in particular). The WO 90/14837 publication teaches that by changing the physical parameters and emulsion composition, oil droplet sizes can be change from 1 micron to less than 0.2 microns (See page 43, in particular). The reference emulsion is formulated as a mixture of the oily vehicle and the aqueous phase immunogen as to form oil-in-water (see abstract, claim 1 of WO 90/14837 publication, in particular). Claim 1 is included in this rejection because a composition is a composition irrespective of where the composition is being store and the length of time in storage. The stability and integrity of the composition are the inherent properties of the reference immunogenic composition.

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

17. Claims 35, 40, 43, 46-52, 54-55, 57-63, and 65-72 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 90/14837 publication (December 1990, PTO 1449) in view of Pat No. 5,468,494 A (Nov 1995, PTO 1449).

The teachings of WO 90/14837 publication have been discussed supra.

The claimed invention in claims 40 and 72 differs from the reference only that the oily vehicle is Montanide type ISA 703.

The claimed invention in claim 43 differs from the teachings of the reference only that the immunogenic composition wherein the aqueous immunogen comprises a gastin-17 (G-17), a gastrin-34(G34) or gonadotropin releasing hormone immunomimic peptide conjugated to an immunogenic carrier protein optionally linked through a spacer peptide.

The claimed invention in claim 46 differs from the teachings of the reference only that the immunogenic composition wherein the immunogen comprises a synthetic immunomimic peptide conjugated to an immunogenic carrier component.

The claimed invention in claims 47 and 71 differs from the teachings of the reference only that the method wherein the peptide comprises an epitope of gastrin 17 (G17) a gastrin-34(G34) or GnRH.

The claimed invention in claim 48 differs from the teachings of the reference only that the method wherein the aqueous phase immunogen comprises an immunogenic carrier conjugated to an immunomimic peptide.

The claimed invention in claim 49 differs from the teachings of the reference only that the method wherein the frozen storage stability of the immunogenic emulsion comprises a prolonged integrity of the immunogen.

The claimed invention in claim 50 differs from the teachings of the reference only that the method wherein the integrity of is preserved more than one week.

The claimed invention in claim 51 differs from the teachings of the reference only that the method wherein the integrity of is preserved more than one month.

The claimed invention in claim 52 differs from the teachings of the reference only that the method wherein the integrity of is preserved more than one year.

The claimed invention in claim 54 differs from the teachings of the reference only that the immunogenic composition wherein the immunogen remains substantially intact after prolonged frozen storage.

The claimed invention in claim 55 differs from the teachings of the reference only that the immunogenic composition wherein the immunogen is not significantly affected after one or more freeze-thaw cycles.

The claimed invention in claim 57 differs from the teachings of the reference only that the immunogenic composition wherein the immunogen release rate from the emulsion is not significantly altered by long-term frozen storage.

The claimed invention in claim 58 differs from the teachings of the reference only that the immunogenic composition wherein the immunogen is a synthetic immunomimic peptide conjugated to an immunogenic carrier.

The claimed invention in claims 59 and 65 differs from the teachings of the reference only that the immunogenic composition is stored at about -18 °C to about -80°C.

The claimed invention in claims 60, and 66 differs from the teachings of the reference only that the immunogenic composition is stored at about -18°C to about -23°C.

The claimed invention in claims 61, and 67 differs from the teachings of the reference only that the immunogenic composition is stored at about -70°C.

The claimed invention in claim 62 from the teachings of the reference only that the method wherein the frozen storage comprises preparing an immunogenic oil-in-water and water-in-oil emulsion by mixing an aqueous phase immunogen comprising an immunogenic carrier conjugated to a G17 immunomimic peptide with a pharmaceutically acceptable oily vehicle consisting of a Montanide type ISA 703 without an additional emulsion stabilizer; the thawed composition retaining at least 60% of the emulsion globules at a size of less than 1 μm and exhibiting a normal release rate of the immunogen.

The claimed invention in claim 63 from the teachings of the reference only that the method wherein the immunogen comprises significant gain of immunogenicity.

The claimed invention in claim 68 from the teachings of the reference only for a method for stable storage of an immunogenic emulsion comprising storing at a temperature ranging from about -18 °C to about -80°C an aqueous phase immunogenic carrier conjugated to an peptide in a mixture with an oily vehicle selected from the group consisting of the Montanide ISA 703 without an additional emulsion stabilizer; the thawed composition retaining at least 60% of the emulsion globules at a size of less than 1 μm and exhibiting a normal release rate of any immunogen.

The claimed invention in claim 69 from the teachings of the reference only that the method wherein the immunogenic carrier comprises diphtheria toxoid, tetanus toxoid and keyhole limpet hemocyannin.

The '494 patent teaches an immunogenic composition comprising an emulsion such as oily vehicle Montanide ISA type 703 and an aqueous immunogen such as gastrin 17 conjugated to an immunogenic carrier such as diphtheria toxoid, tetanus toxoid and keyhole limpet hemocyannin in PBS and aluminum monostereate (See column 4, example 4, claims 1-5 of '494 patent, in particular). The '494 patent further teaches a method for formulating the reference immunogenic composition by mixing an aqueous immunogen such as gastrin 17, which is a hormone immunomimic peptide fragment, coupled to an immunogenic carrier component such as DT in PBS with a pharmaceutically acceptable oily vehicle in an oil-in-water or water-in-oil formulation wherein the suitable oily vehicle is Montanide type ISA 703 (See column 4, lines 25-65, in particular). The reference method of formulating the reference immunogenic composition is stable in storage for a minimal of several weeks, which is more than one day or at least one month (see column 4, lines 37-40, in particular). The term "comprising" is open-ended. It expands the claimed immunogenic composition to include additional compound in the composition. The claimed composition appears to be the same as the reference composition. The reference composition is stable in cold storage that can last at least 8 days, a year, or in freezing temperature because of the inherent property of the reference mineral oil, Montanide type ISA 703. The increase in immunogenicity upon storage is also an inherent property of the reference mineral oily vehicle Montanide type ISA 703 in composition. The '494 patent teaches that the conjugate is more immunogenic in terms of both potency and the duration of anti-hG17 antibody response because it possesses a superior spacer element (See column 6, lines 10-25, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the immunogen as taught by the WO 90/14837 publication for the immunogen such as gastrin 17 conjugated to an immunogenic carrier such as diphtheria toxoid, tetanus toxoid or keyhole limpet hemocyannin as taught by the '494 patent for a method of making an immunogenic emulsion which is stable in frozen storage as taught by the WO 90/14837 publication and the '494 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '494 patent teaches that the conjugate is more immunogenic (significant gain of immunogenicity) in terms of both potency and the duration of anti-hG17 antibody response because it possesses a superior spacer element (See column 6, lines 10-25, in particular). The WO 90/14837 publication teaches that any metabolizable oil and an emulsifying agent which is also an immunostimulating agent is useful as an adjuvant formulation (enhance immunogenicity) and by changing the physical parameters and emulsion composition, oil droplet sizes can be change from 1 micron to less than 0.2 microns (See abstract, and page 43, in particular). The method of storing or preserving any immunogenic composition in a freezer until use such as having a temperature about -18 °C to about -80°C is within the purview of one ordinary skill in the art the time the invention as taught by the '494 patent (See column 6, line 55, in particular). The functional limitation of exhibiting a normal release rate of the immunogen is an inherent property of the reference emulsion as taught by the WO 90/14837 publication.

18. Claims 53, 56 and 64 appear to be free of prior art.

19. No claim is allowed.

20. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner

can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

22. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

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